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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,587	10/02/2006	Jaime Moscoso Del Prado	4716IF-2	1153

22442 7590 04/28/2009

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,587	MOSCOSO DEL PRADO ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 29-32* is/are pending in the application.

4a) Of the above claim(s) *6,13-15 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12,16-22 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/2/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/6/2007; 10/2/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Examiner acknowledges the election, with traverse, of Group I directed to liposomal formulations, in the reply filed on 14 April 2009. In addition, the applicant elected the following components which together form the elected species of liposomal formulations: (1) 5FU hydrophilic agent, (2) DSPC neutral saturated phospholipid, and (3) DSPG charged saturated lipid.

The applicant has traversed the restriction requirement, suggesting that there is no search burden and the search for Group I would overlap with the search for Group II.

The Lack of Unity restriction requirement was based upon disclosure of claim 1 by prior art. There being no special technical feature, as required for co-examination, the restriction is deemed proper.

Accordingly, the examiner finds the applicant's traversal unpersuasive and therefore makes the restriction final.

Claim Status

Claims 1-22 and 29-32 are pending. However, claims 6, 13-15 and 29-31 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claim 32 is newly added. Claims 1-5, 7-12, 16-22 and 32 are under current examination.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 2 October 2006 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 7 August 2007 and 2 October 2006 consisting of 5 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims as a 371 of PCT/ES05/00171 (filed 04/01/2005). The application also claims benefit from foreign applications SPAIN P200400826 (filed 4/2/2004) and SPAIN P200402862 (filed 11/26/2004). The instant application has been granted the benefit date, 2 April 2004, from the foreign application SPAIN P200400826.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7-10, 16-19, 22 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Webb et al (US2005/0118249).

Claim 1 is directed to a pharmaceutical or veterinary formulations comprising at least one active hydrophilic agent encapsulated in liposomes composed of at least one lipid bilayer formed by a mixture of at least one neutral saturated phospholipid and at least one charged saturated lipid. Webb et al. teach liposomes comprising a neutral saturated phospholipid (DSPC) and a negatively charged saturated lipid (DSPG) and Cholesterol and an active hydrophilic agent (Floxuridine). Webb et al. indicate that this formulation was administered to rodents, therefore, the examiner concludes it is at least a veterinary formulation.

Claim 2 is directed to the pharmaceutical or veterinary formulations according to claim 1, wherein the neutral saturated phospholipid is selected from the group consisting of derivatives of phosphatidylcholine and their combinations. Webb et al. teach DSPC which is a derivative of phosphatidylcholine.

Claim 3 is directed to the pharmaceutical or veterinary formulations according to claim 2, wherein the derivative of phosphatidylcholine is selected from the group consisting of DSPC, DPPC and DMPC. Webb et al. teach DSPC (distearoylphosphatidylcholine).

Claim 4 is directed to the pharmaceutical or veterinary formulations according to claim 1, wherein a negatively charged saturated lipid of said charged saturated lipid is selected from the group consisting of derivatives of phosphatidylglycerol, phosphatidylserine, phosphatidylinositol, phosphatidic acid and their combinations. Webb et al. teach DSPC which is a derivative of phosphatidylcholine.

Claim 5 is directed to the pharmaceutical or veterinary formulations according to claim 4, wherein the negatively charged saturated lipid is selected from the group consisting of DSPG, DPPG, and PS. Webb et al. teach DSPG (distearoyl phosphatidyl glycerol).

Claim 7 is directed to the pharmaceutical or veterinary formulations according to claim 1 further comprising at least one other lipid selected from the group consisting of sterols and derivatives, gangliosides and sphingomyelins. Webb et al. teach liposomes further comprising the sterol, cholesterol.

Claim 8 is directed to the pharmaceutical or veterinary formulations according to claim 7, wherein the sterol is cholesterol. Webb et al. teach the particular sterol, cholesterol.

Claim 9 is directed to the pharmaceutical or veterinary formulations according to claim 1, wherein the active hydrophilic agent is a drug. Webb et al. teach the active hydrophilic agent drug, Floxuridine.

Claim 10 is directed to the pharmaceutical or veterinary formulations according to claim 9, wherein the drug has low molecular weight. Floxuridine is a drug that has low molecular weight.

Claim 16 is directed to the pharmaceutical or veterinary formulations according to claim 1, wherein the bilayer lipid has a neutral saturated phospholipid/charged saturated lipid molar ratio between 50/50 and 95/5. Webb et al. teach liposomes of DSPC:DSPG:Cholesterol having a molar ratio of 70:20:10.

Claim 17 is directed to the pharmaceutical or veterinary formulations according to claim 16, wherein the bilayer lipid has a neutral saturated phospholipid/charged saturated lipid molar ratio between 80/20 and 95/5. Webb et al. teach liposomes of DSPC:DSPE having a molar ratio of 95:5.

Claim 18 is directed to the pharmaceutical or veterinary formulations according to claim 1, wherein the active hydrophilic agent/lipids molar ration is between 0.01/1 and 40/1. Webb et al. teach "drug-to-lipid weight ratio was 0.1:1" (parag.0024).

Claim 19 is directed to the pharmaceutical or veterinary formulations according to claim 18, wherein the active hydrophilic agent/lipids molar ration is between 0.1/1 and 2/1. Webb et al. teach "drug-to-lipid weight ratio was 0.1:1" (parag.0024).

Claim 22 is directed to the pharmaceutical or veterinary formulations according to claim 1 further including a pharmaceutically acceptable vehicle. Webb et al. teach their

compositions further comprise at least one pharmaceutically acceptable excipient (claim 11).

Claim 32 is directed to the pharmaceutical or veterinary formulations according to claim 1 formulated for topical administration. Since the limitation "for topical administration" seems to be an intended use, the examiner believes the formulations of Webb et al. satisfy this limitation.

Accordingly, Webb et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 12, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al (US2005/0118249) as applied to claims 1, 9 and 10 above.

Claims 11, 12, 20 and 21 are directed to pharmaceutical or veterinary formulations which comprise the particular active hydrophilic agent (drug), 5-fluorouracil.

Claims 11, 12, 20 and 21 are dependent from claims 1, 9 and 10. The teachings of Webb et al. which encompass the limitations of claims 1, 9 and 10 are described above in the 35 USC 102(e) rejection.

While Webb et al. teaches the genus of pharmaceutical or veterinary formulations which comprise an active hydrophilic agent (drug) and many particulars of the claimed limitations, such as molar ratios of lipids and drug/lipids, Webb et al. do not teach a specific embodiment of formulations comprising 5-fluorouracil.

However, Webb et al. teach "liposomes of the invention contain an encapsulated biologically active agent...the biologically active agent is a drug and most preferably an anti-neoplastic agent...Examples of some of the antineoplastic agents which can be loaded into liposomes...[are] 5-fluorouracil" (paragraphs 0058-0059).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to provide pharmaceutical or veterinary formulations comprising at least one active hydrophilic agent encapsulated in liposomes composed of at least one lipid bilayer formed by a mixture of at least one neutral saturated phospholipid and at least one charged saturated lipid, wherein the active hydrophilic agent is 5-fluorouracil.

The person of ordinary skill in the art would have been motivated to select the particular embodiment of pharmaceutical or veterinary formulations comprising 5-fluorouracil because Webb et al. suggest this agent (5-FU) was a suitable alternative for the particular drugs described in their exemplary embodiments. Furthermore, the lipid and drug ratios of claims 20-21 would be obvious because Webb et al. suggest these general ratios. The embodiment of claim 12 having DSPC:DSPG:5-FU would be obvious because Webb et al. suggests the liposomal combination DSPC:DSPG and also suggest liposomes with 5-FU. Taken together, a skilled artisan would envision the embodiment, DSPC:DSPG:5-FU, because there are a limited number of options described by Webb.

The skilled artisan would have had a reasonable expectation of success in producing pharmaceutical or veterinary formulations comprising 5-fluorouracil because Webb et al. teach they can produce several similar compositions, suggesting it would be predictable to produce a liposomal composition comprising 5-FU.

Therefore the composition as taught by Webb et al. would have been *prima facie* obvious over the composition of the instant application.

Claims 1-5, 7-12, 16-22 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al (US2005/0118249) in view of da Costa et al. (Acta Scientiarum Technology. 2003; 25(1): 53-61).

The teachings of Webb et al. are described above in the previous 35 USC 102 & 103 rejections.

Webb et al. teaches the genus of pharmaceutical or veterinary formulations which comprise an active hydrophilic agent (drug) and many particulars of the claimed limitations, such as molar ratios of lipids and drug/lipids. Webb et al. further suggests a specific embodiment of liposomal formulations comprising 5-fluorouracil.

Webb et al. does not teach topical administration of liposomes, as recited by claim 32.

However, da Costa et al. teach encapsulation of 5-fluorouracil in liposomes for topical administration.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to provide pharmaceutical or veterinary formulations comprising at least one active hydrophilic agent encapsulated in liposomes composed of at least one lipid bilayer formed by a mixture of at least one neutral saturated phospholipid and at least one charged saturated lipid, wherein the formulation is for topical administration. Furthermore, it would be obvious to formulate a liposome comprising the active hydrophilic agent, 5-fluorouracil.

The person of ordinary skill in the art would have been motivated to select the particular embodiment of pharmaceutical or veterinary formulations comprising 5-fluorouracil for topical administration because da Costa et al. teach encapsulation of 5-fluorouracil in liposomes for topical administration.

The skilled artisan would have had a reasonable expectation of success in producing pharmaceutical or veterinary formulations comprising 5-fluorouracil because Webb et al. teach they can produce several similar compositions, suggesting it would be predictable to produce a liposomal composition comprising 5-FU. Furthermore, da Costa et al. teach encapsulation of 5-fluorouracil in liposomes for topical administration.

Therefore the composition as taught by Webb et al. in view of da Costa would have been *prima facie* obvious over the composition of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633